JGP

The Journal of General Physiology
Vol 133 • No 1 • January 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

ARTICLES

1 **Local anesthetics disrupt energetic coupling between the voltage-sensing segments of a sodium channel.** Yukiko Muroi and Baron Chanda

17 **Regulated RNA editing and functional epistasis in *Shaker* potassium channels.** Lindsey Ingleby, Rachel Maloney, James Jepson, Richard Horn, and Robert Reenan

29 **Identification of regulatory phosphorylation sites in a cell volume– and Ste20 kinase–dependent ClC anion channel.** Rebecca A. Falin, Rebecca Morrison, Amy-Joan L. Ham, and Kevin Strange

43 **Blocking pore-open mutants of CLC-0 by amphiphilic blockers.** Xiao-Dong Zhang, Pang-Yen Tseng, Wei-Ping Yu, and Tsung-Yu Chen

59 **Amphiphilic blockers punch through a mutant CLC-0 pore.** Xiao-Dong Zhang and Tsung-Yu Chen

69 **Mutations at the signature sequence of CFTR create a Cd^{2+}-gated chloride channel.** Xiaohui Wang, Silvia G. Bompadre, Min Li, and Tzyh-Chang Hwang

79 **The skeletal L-type Ca^{2+} current is a major contributor to excitation-coupled Ca^{2+} entry.** Roger A. Bannister, Isaac N. Pessah, and Kurt G. Beam

93 **Voltage- and [ATP]-dependent gating of the $P2X_2$ ATP receptor channel.** Yuichiro Fujiwara, Batu Keceli, Koichi Nakajo, and Yoshihiro Kubo

111 **Molecular basis for cation selectivity in claudin-2–based paracellular pores: identification of an electrostatic interaction site.** Alan S.L. Yu, Mary H. Cheng, Susanne Angelow, Dorothee Günzel, Sanae A. Kanzawa, Eveline E. Schneeberger, Michael Fromm, and Rob D. Coalson

Cover picture: Genomic organization of the *Drosophila Shaker* locus (top) showing alternative splicing (dashed lines) and evolutionarily conserved noncoding intron sequences (e1–e3) that direct four ADAR-mediated RNA editing sites in *Shaker* transcripts. These sites reassign encoded amino acids at four highly conserved positions (1–4), depicted on the Kv channel membrane topology (bottom left). Temporal regulation (bottom right) of the levels of editing of the four *Shaker* RNA editing sites during stages of development (see article by Ingleby et al., 17–27).

JGP

The Journal of General Physiology
Vol 133 • No 2 • February 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

EDITORIALS

129 **Kudos to reviewers for the *JGP*: you make our science better.** Edward N. Pugh, Jr., Editor

ARTICLES

131 **Intracellular proton-transfer mutants in a CLC Cl^-/H^+ exchanger.** Hyun-Ho Lim and Christopher Miller

139 **Measuring the influence of the BK_{Ca} β1 subunit on Ca^{2+} binding to the BK_{Ca} channel.** Tara-Beth Sweet and Daniel H. Cox

151 **Decremental response to high-frequency trains of acetylcholine pulses but unaltered fractional Ca^{2+} currents in a panel of "slow-channel syndrome" nicotinic receptor mutants.** Sergio Elenes, Michael Decker, Gisela D. Cymes, and Claudio Grosman

171 **Pentobarbital produces activation and block of $\alpha_1\beta_2\gamma_{2S}$ $GABA_A$ receptors in rapidly perfused whole cells and membrane patches: divergent results can be explained by pharmacokinetics.** Kevin J. Gingrich, Paul M. Burkat, and William A. Roberts

189 **Four Ca^{2+} ions activate TRPM2 channels by binding in deep crevices near the pore but intracellularly of the gate.** László Csanády and Beáta Törőcsik

205 **Dynamic coupling of voltage sensor and gate involved in closed-state inactivation of Kv4.2 channels.** Jan Barghaan and Robert Bähring

225 **Correction**

Cover picture: TRPM2 closure is slowed by extracellular Ca^{2+} entry through the channel pore. (Left) Current decay upon rapid removal of intracellular Ca^{2+} is much slower when extracellular Ca^{2+} is high. (Right) Interpretation. (Top) Without extracellular Ca^{2+}, the activating sites rapidly lose Ca^{2+} and quickly close. (Bottom) In high extracellular Ca^{2+}, the activating sites, located in a deep vestibule of the channel, remain liganded longer due to Ca^{2+} entry through the open pore (see article by Csanády and Törőcsik, 189–203).

JGP

The Journal of General Physiology
Vol 133 • No 3 • March 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

PERSPECTIVES

227 **Perspectives on TRP channel structure and the TRPA1 puzzle.** Ramon Latorre, Guest Editor

231 **Divide and conquer: high resolution structural information on TRP channel fragments.** Rachelle Gaudet

239 **Hot on the trail of TRP channel structure.** Vera Y. Moiseenkova-Bell and Theodore G. Wensel

245 **TRPA1 and cold transduction: an unresolved issue?** Ombretta Caspani and Paul A. Heppenstall

251 **Burning cold: involvement of TRPA1 in noxious cold sensation.** Kelvin Y. Kwan and David P. Corey

257 **Polymodal ligand sensitivity of TRPA1 and its modes of interactions.** Sangsu Bang and Sun Wook Hwang

ARTICLES

263 **N-terminal inactivation domains of β subunits are protected from trypsin digestion by binding within the antechamber of BK channels.** Zhe Zhang, Xu-Hui Zeng, Xiao-Ming Xia, and Christopher J. Lingle

283 **Mechanism of increased BK channel activation from a channel mutation that causes epilepsy.** Bin Wang, Brad Rothberg, and Robert Brenner

295 **KirBac1.1: it's an inward rectifying potassium channel.** Wayland W.L. Cheng, Decha Enkvetchakul, and Colin G. Nichols

307 **Evidence for a proton–protein symport mechanism in the anthrax toxin channel.** Daniel Basilio, Stephen J. Juris, R. John Collier, and Alan Finkelstein

315 **CFTR functions as a bicarbonate channel in pancreatic duct cells.** Hiroshi Ishiguro, Martin C. Steward, Satoru Naruse, Shigeru B.H. Ko, Hidemi Goto, R. Maynard Case, Takaharu Kondo, and Akiko Yamamoto

327 **Disruption of the IS6-AID linker affects voltage-gated calcium channel inactivation and facilitation.** Felix Findeisen and Daniel L. Minor Jr.

345 Correction

Cover picture: Accessibility to trypsin digestion of BK channel β-subunit N termini reveals their sequestration in the channel antechamber. (Top) Schematic of the pathway for access of the β2 N-terminal inactivation domain to the BK channel central cavity. (Bottom) Model of the hypothesis that N termini transiently bind in the antechamber between the pore and cytosolic domains, resulting in reduced rates of trypsin digestion even in closed channels (see article by Zhang et al., 263–282).

JGP

The Journal of General Physiology
Vol 133 • No 4 • April 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

ARTICLES

347 **Fluorescence changes reveal kinetic steps of muscarinic receptor–mediated modulation of phosphoinositides and Kv7.2/7.3 K^+ channels.** Jill B. Jensen, John S. Lyssand, Chris Hague, and Bertil Hille

361 **Control of voltage-gated K^+ channel permeability to $NMDG^+$ by a residue at the outer pore.** Zhuren Wang, Nathan C. Wong, Yvonne Cheng, Steven J. Kehl, and David Fedida

375 **The analysis of desensitizing CNGA1 channels reveals molecular interactions essential for normal gating.** Monica Mazzolini, Claudio Anselmi, and Vincent Torre

387 **Arachidonic acid inhibition of L-type calcium ($Ca_V1.3b$) channels varies with accessory $Ca_V\beta$ subunits.** Mandy L. Roberts-Crowley and Ann R. Rittenhouse

405 **State-dependent modulation of CFTR gating by pyrophosphate.** Ming-Feng Tsai, Hiroyasu Shimizu, Yoshiro Sohma, Min Li, and Tzyh-Chang Hwang

421 **SLC26A9 is a constitutively active, CFTR-regulated anion conductance in human bronchial epithelia.** Carol A. Bertrand, Ruilin Zhang, Joseph M. Pilewski, and Raymond A. Frizzell

439 **Elevations of intracellular calcium reflect normal voltage-dependent behavior, and not constitutive activity, of voltage-dependent calcium channels in gastrointestinal and vascular smooth muscle.** John G. McCarron, Marnie L. Olson, Susan Currie, Amanda J. Wright, Kurt I. Anderson, and John M. Girkin

459 Correction

Cover picture: Fluorescence changes reveal rapid interactions between muscarinic receptor (M_1R) and G proteins during receptor activation. (Top) Cartoon of expressed proteins in membrane: fluorescently labeled M_1R-CFP and $G\beta_1$-YFP and unlabeled $G\alpha_q$ and $G\gamma_2$. (Middle) Kinetics of $M_1R/G\beta_1$ interaction in a single cell. Blue and orange lines are fluorescence from M_1R-CFP and $G\beta_1$-YFP and the black line is their ratio. (Bottom) Averaged FRET timecourse from several cells (see article by Jensen et al., 347–359).

JGP

The Journal of General Physiology
Vol 133 • No 5 • May 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

EDITORIALS

461 **Editorial.** Edward N. Pugh Jr.

COMMENTARIES

463 **Uncooperative Voltage Sensors.** Richard Horn

ARTICLES

467 **A single charged voltage sensor is capable of gating the *Shaker* K^+ channel.** Dominique G. Gagnon and Francisco Bezanilla

485 **Channel-like slippage modes in the human anion/proton exchanger ClC-4.** Alexi K. Alekov and Christoph Fahlke

497 **Ionic selectivity in L-type calcium channels by electrostatics and hard-core repulsion.** Dezső Boda, Mónika Valiskó, Douglas Henderson, Bob Eisenberg, Dirk Gillespie, and Wolfgang Nonner

511 **DHPR activation underlies SR Ca^{2+} release induced by osmotic stress in isolated rat skeletal muscle fibers.** James D. Pickering, Ed White, Adrian M. Duke, and Derek S. Steele

525 **Intracellular calcium strongly potentiates agonist-activated TRPC5 channels.** Nathaniel T. Blair, J. Stefan Kaczmarek, and David E. Clapham

Cover picture: Snapshot of a reduced model of a selectivity filter of an L-type calcium channel that fits a surprising range of data although it has no preformed binding sites. The filter contains eight half-charged oxygens (red, radius 1.4 Å) , representing EEEE side chains mobile within the filter. Ions are spheres with their crystal radii, Ca^{2+} (green, 0.99 Å), Na^+ (blue, 0.95 Å). Upper schematic, transverse view; lower, axial view (see article by Boda et al., 497-509).

JGP

The Journal of General Physiology
Vol 133 • No 6 • June 2009

General Physiology is the study of biological mechanisms through analytical investigations, which decipher the molecular and cellular mechanisms underlying biological function at all levels of organization.

The mission of the *Journal of General Physiology* is to publish articles that elucidate important biological, chemical, or physical mechanisms of broad physiological significance.

EDITORIALS

547 **A Challenge to Goliath.** Mike Rossner

COMMENTARIES

549 **Gating on the outside.** Andrew L. Harris

ARTICLES

555 **Conformational changes in a pore-forming region underlie voltage-dependent "loop gating" of an unapposed connexin hemichannel.** Qingxiu Tang, Terry L. Dowd, Vytas K. Verselis, and Thaddeus A. Bargiello

571 **Protein kinase A–dependent modulation of Ca^{2+} sensitivity in cardiac and fast skeletal muscles after reconstitution with cardiac troponin.** Douchi Matsuba, Takako Terui, Jin O-Uchi, Hiroyuki Tanaka, Takao Ojima, Iwao Ohtsuki, Shin'ichi Ishiwata, Satoshi Kurihara, and Norio Fukuda

583 **Mechanism of olfactory masking in the sensory cilia.** Hiroko Takeuchi, Hirohiko Ishida, Satoshi Hikichi, and Takashi Kurahashi

603 **CO_2-induced ion and fluid transport in human retinal pigment epithelium.** Jeffrey Adijanto, Tina Banzon, Stephen Jalickee, Nam S. Wang, and Sheldon S. Miller

LETTERS TO THE EDITOR

623 **TRPA1: the species difference.** Jun Chen and Philip R. Kym

Cover picture: Retinal photoreceptor metabolism increases in the dark, leading to increased deposition of CO_2 and water into the subretinal space (SRS). The retinal pigment epithelium can mitigate this potentially catastrophic metabolic load by increasing CO_2/HCO_3, Na, and H_2O absorption from the SRS into the choroidal blood supply via Na-linked HCO_3 transporters, thus preventing SRS acidosis and retinal detachment (see article by Adijanto et al., 603–622).